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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JONATHAN W. NYCE

Appeal 2008-0636
Application 10/072,010
Application Publication 2002/0119936
Technology Center 1600

Decided : June 23, 2008

Before: FRED E. McKELVEY, *Senior Administrative Patent Judge*, and RICHARD E. SCHAFER, and SALLY GARDNER LANE *Administrative Patent Judges*.

LANE, *Administrative Patent Judge*.

DECISION ON APPEAL

I. STATEMENT OF THE CASE

This is an appeal from a Final Rejection of all of the pending claims: claims 160-162, 165, and 187-190. 35 U.S.C. § 134. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

The involved application was filed October 25, 2001, and published as Patent Application Publication 2002/0119936 ("Pub. 2002/0119936") on

August 29, 2002. The real party-in-interest is said to be East Carolina University. (App. Br. 1).

The Examiner relied on the following U.S. patents:

Name	Patent No.	Date Issued	Abbreviation
Prendergast	4,956,355	Sep. 11, 1990	"Prendergast"
Nyce	5,527,789	Jun. 18, 1996	"Nyce"

The Examiner also relied on the following publications:

Pharmaceutical Dosage Forms 110 (Herbert A. Lieberman, et al. eds., 1990) ("Lieberman");

Remington: The Science and Practice of Pharmacy 1505 (Alfonson R. Gennaro, ed., 1985) ("Remington"); and

H. William Kelly and Malcolm R. Hill, "Chapter 24/Asthma," *Pharmacology – A Pathophysiologic Approach* 408-49 (1992) ("Kelly").

Appellant has not disputed the prior art status of any of these references.

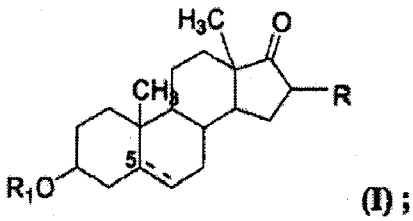
Appellant appeals (1) the rejection of claims 160-162 under 35 U.S.C. § 103(a) over the combination of the teachings of Prendergast, Lieberman, and Remington; (2) the rejection of claims 187-189 under 35 U.S.C. § 103(a) over the combination of the teachings of Prendergast, Lieberman, Remington, and Kelly; and (3) the rejection of claims 160-162, 165, and 187-190 under 35 U.S.C. § 103(a) over the combination of the teachings of Nyce, Lieberman, Remington, and Kelly. Appellant argued separately against the rejection of claims 165 and 190 over the teaching of Nyce, Lieberman, Remington, and Kelly. (App. Br. 15). We review only a representative claim for each of the other rejections. 37 C.F.R. § 41.37(c)(1)(vii).

II. FINDINGS OF FACT

The record supports the following findings of fact, as well as any other findings of fact set forth in this decision, by a preponderance of the evidence.

1. Appellant's claim 160 recites:

> A pharmaceutical composition, comprising a carrier and an amount of an active agent effective for treatment of bronchoconstriction, lung inflammation, lung allergy, or asthma selected from dehydroepiandrosterone, or pharmaceutically or veterinarily acceptable salts thereof, the dehydroepiandrosterone having the chemical formula

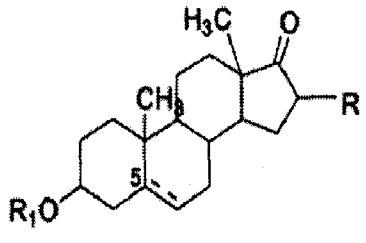


(I);

> wherein the broken line represents a single or double bond; R is hydrogen or halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R_1 is SO_2OM, wherein M is H,
>
> wherein the pharmaceutical composition comprises particles of about 1.0 μm to about 5 μm in size.

2. Appellant's claim 187 recites:

> A pharmaceutical composition, comprising a carrier and an amount of an active agent effective for treatment of bronchoconstriction, lung inflammation, lung allergy, or asthma selected from dehydroepiandrosterone, or pharmaceutically or veterinarily acceptable salts thereof, the dehydroepiandrosterone having the chemical formula



(I);

wherein the broken line represents a single or double bond; R is hydrogen or halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R_1 is SO_2OM, wherein M is H

wherein the pharmaceutical composition comprises particles about 15 μm to about 500 μm in size.

3. Appellant's claim 165 recites:

The pharmaceutical composition of claim 160, further comprising an amount of ubiquinone (CoQn, wherein n=l to 12) effective to reduce adenosine depletion.

4. Appellant's claim 190 recites:

The pharmaceutical composition of claim 187, further comprising an amount of ubiquinone (CoQn, wherein n=l to 12) effective to reduce adenosine depletion in an animal tissue.

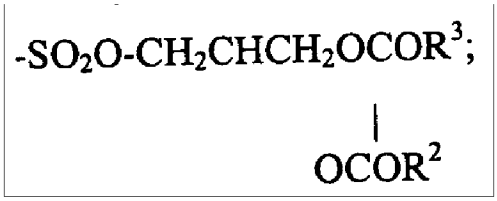
5. Appellant's specification discloses that "the epiandrosterones and their salts are administered in a dosage of about 0.01, about 0.1, about 0.4, about 1, about 5, about 10, about 20 to about 4, about 30, about 70, about 100, about 300, about 600, about 1000, about 2000, about 3600 mg/kg body weight." (Pub 2002/0119936 ¶ [0032]).[1]

[1] We find the dosage statement to be something other than a clear, concise or exact statement. *Cf.* 35 U.S.C. § 112, first paragraph. We construe the statement to mean that the dose is somewhere between 0.01 and 3,600

6. Appellant's specification discloses that "ubiquinone is preferably administered in a total amount per day of about 0.1, about 1, about 5, about 10, about 15, about 30 to about 50, about 100, about 150, about 300, about 600, about 900, about 1200 mg/kg body weight per day." (Pub 2002/0119936 ¶ [0032]).[2]

7. Appellant defines "Dehydroepiandrosterone sulphate" as a compound of formula (I), "wherein R is H, R_1 is SO_2OM and M is a sulphatide group as defined above, and the double bond is absent . . . ." (Pub. 2002/0119936 ¶ [0026]).

8. The sulphatide group referred to in Appellant's definition of dehydroepiandrosterone sulphate is depicted as



(Pub. 2002/0119936 ¶ [0021]).

9. In the specification, Appellant states:

> Clinically, DHEA has been used systemically and/or topically for treating patients suffering from psoriasis, gout, hyperlipemia, and it has been administered to post-coronary patients. In mammals, DHEA has been shown to have weight optimizing and anti-carcinogenic effects, and it has been used clinically in Europe in conjunction with estrogen as an agent to reverse menopausal symptoms and also has been used in the treatment of manic depression, schizophrenia, and Alzheimer's disease. DHEA has also been used clinically at 40 mg/kg/day in

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mg/kg body weight and that one skilled in the art (e.g., a physician) should determine the dose on a case-by-case basis.

[2] The ubiquinone dosage statement is just as confusing as the epiandrosterone dosage statement discussed in the previous footnote.

> the treatment of advanced cancer and multiple sclerosis. Mild androgenic effects, hirsutism, and increased libido were the side effects observed. These side effects can be overcome by monitoring the dose and/or by using analogues.

(Pub. 2002/0119936 ¶ [0009]).

10. Appellant's specification does not elaborate on the doses or analogues that can be used to overcome the stated side effects.

11. Appellant's specification also states:

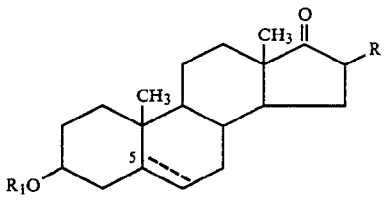
> Thus, although DHEA was once considered a safe drug, it is now predicted that with long term administration of DHEA or its analogues, chronic heart failure may occurs [sic] as a complicating side effect. Further, some analogues of DHEA produce this side effect to a greater extent because, in general, they are more potent inhibitors of G6PDH than DHEA.

(Pub. 2002/0119936 ¶ [0010]).

12. Appellant's specification does not elaborate on the length of the "long term administration of DHEA" that is said to cause chronic heart failure in a patient, or on the specific analogues of DHEA that are said to "produce this side effect to a greater extent" in a patient.

13. Appellant listed Epigenesis Pharmaceuticals, Inc. on the cover sheet of the specification.

14. Prendergast teaches a compound which is the same as the claimed compound and is depicted as



(I)

(Prendergast col. 4, ll. 32-40), the broken line represents a single or double bond (*id.* col. 5, ll. 1-2), R is a hydrogen or bromine atom (*id.* col. 4, l. 42), the H at position 5 is present in the alpha or beta configuration or a mixture of both configurations (*id.* col. 5, ll. 2-3), R_1 is SO_2OM (*id.* col. 5, l. 18), and M is hydrogen or sodium (*Id.* col. 4, ll. 43-44).

15. Prendergast teaches dehydroepiandrosterone, "wherein R and R1 are each hydrogen and the double bond is present." (Prendergast col. 5, ll. 8-10).

16. Prendergast teaches that "[s]uitable formulations for oral administration include . . . inhalations . . . ." (Prendergast at col. 5, ll. 46-49).

17. Prendergast teaches that "[t]he compound of formula (I) may also be administered in the form of an infusion solution or as a nasal inhalation or spray." (Prendergast col. 5, ll. 61-64).

18. Prendergast teaches that the pharmaceutical formulation disclosed is administered "from [sic] to 1,000 mg of active ingredient. Preferably, each unit dose comprises from 50 to 500 mg of active ingredient." (Prendergast col. 5, ll. 65-68).

19. In Example 9, Prendergast describes treatment with dehydroepiandrosterone (abbreviated as "DHEA") of 12 AIDS patients for "up to six months." (Prendergast col. 13, ll. 48-51).

20. Prendergast reports in Example 9 that "[t]he DHEA was administered in the form of hard gelatin capsules continuing 100 mg of DHEA and at a rate of 100 mg to 600 mg per day. The vast majority being on 500 mg per day in divided doses." (Prendergast col. 13, ll. 51-55).

21. Prendergast reports in Example 9 that

> Compounds of the formula (I) and, in particular, dehydroepiandrosterone and the derivatives thereof hereinbefore mentioned have particular advantages in the treatment of patients infected with HIV. Particular advantages of such compounds include the virtual absence of toxicity . . . .
>
> Dehydroepiandrosterone has demonstrated a complete lack of adverse physical, biochemical or hematological effects in twelve subjects who received daily doses of up to 600 mg for up to six months.

(*Id.* at col. 14, ll. 3-13).

22. Remington relates to inhalational drug delivery. (Remington 1505).

23. Remington teaches that "particle size is of major importance in the administration of this type of [inhalation] preparation. . . . It has been reported in the literature that the optimum particle size for penetration into the pulmonary cavity is of the order of ½ to 7 μm." (Remington 1505).

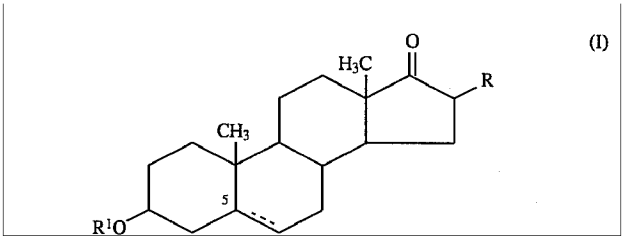
24. Lieberman teaches that size reduction of pharmaceuticals has advantages, such as enhanced bioavailability. (Lieberman 110).

25. Kelly relates to "Aerosol Therapy for Asthma." (Kelly 432).

26. Kelly teaches that "[d]evices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35 μm in diameter." (Kelly 432).

27. Nyce relates to the administration of ubiquinone to combat dehydroepiandrosterone-induced heart failure in cancer patients. (Nyce abstract).

28. The dehydroepiandrosterone disclosed in Nyce has the formula:



"wherein R is hydrogen or a halogen; and R_1 is hydrogen or an SO_2OM group where M is hydrogen, sodium, a sulphatide group

$$-SO_2O-CH_2\underset{\displaystyle OCOR^2}{\underset{|}{C}}HCH_2OCOR^3$$

. . . and the broken line represents an optional double bond, and the hydrogen atom at position 5 is present in the alpha or beta configuration or the compound comprises a mixture of both configurations . . . ." (Nyce col. 2, l. 48, through col. 3, l. 21).

29. Nyce teaches that "[t]he ubiquinone is preferably administered in a total amount per day of about 1 to 1200 mg/kg body weight, … most preferably about 50 to 150 mg/kg." (Nyce col. 5, ll. 63-66).

30. Nyce teaches that formulations that include DHEA or DHEA analogs "include those suitable for . . . nasal . . . administration. (Nyce col. 6, ll. 35-43).

31. Nyce teaches that "[n]asal spray formulations comprise purified aqueous solutions of the active compound . . . . preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes." (Nyce col. 7, ll. 17-21).

32. Appellant filed a Declaration pursuant to 37 C.F.R. § 1.132 executed by Dr. Cynthia Robinson, M.D., on March 14, 2005 ("Robinson Decl."). (*See* App. Br. 8).

33. Dr. Robinson represented that she is Vice President of Clinical Development at Epigenesis Pharmaceuticals, L.L.C. (Robinson Decl. at 1).

34. Dr. Robinson testified:

> In our hands, use of respirable dehydroepiandrosterone-sulfate (DHEA-S) produces the unexpected results of low systemic absorption without systemic effects as observed in the toxicology studies described below. I include below one animal study and two human studies, which demonstrate the efficacy of, inhaled DHEA-S in treating asthma, while producing minimal systemic side-effects. The particle size of the DHEA-S in the formulations used in these studies was about 1 μm to about 5 μm. All these experiments were performed under my supervision.

(Robinson Decl. ¶ 3, p. 2).

35. Dr. Robinson did not discuss or include the results of studies using DHEA-S formulated to any other particle size.

36. Dr. Robinson testified:

> The lungs receive a quarter of the cardiac output every minute, and the lung is separated from the blood stream by about one cell diameter at the alveolar level. Therefore, the lung has a massive surface area that can be used to dose the systemic circulation. However, in the three studies described below, only a modest increase in circulating DHEA-S was observed. Furthermore, the minimal increase in circulating levels produced minimal adverse effects on humans and animals, thus being counterintuitive that lung dosing produces systemic exposure.

(Robinson Decl. ¶ 4, p. 2).

37. Referring to the first experiment in her declaration, Dr. Robinson stated: "In an animal study we investigated the potential toxicity and toxicokinetics of DHEA-S during daily inhalation administration to dogs

for 13 consecutive weeks followed by a 4-week recovery period." (Robinson Decl. ¶ 5, p. 2).

38. In the study involving dogs, Dr. Robinson reported that DHEA-S was administered at 0, 0.25, 1.00, or 4.00 mg/kg/day. (Robinson Decl. ¶ 5, Table 1, p. 2).

39. Dr. Robinson reported:

> Both the C_{max} and AUC values of DHEA-S generally displayed dose response relationships on both sampling occasions, with little to no overlapping between dose groups. DHEA analysis revealed no obvious relationship between C_{max} and dose with observed peak concentrations generally occurring 1 hour post dose. C_{max} and AUC values showed only slight increasing trends with increasing dose levels. Exposure to DHEA-S generally increased on Day 90 when compared to Day 1, after accounting for the different dose levels administered on Day 1 and 90 for Group 4. Inter-individual variability in exposure, however, was high and some overlapping did exist. Exposure to DHEA, however, did not show any consistent sign of accumulation after repeated dosing.

(Robinson Decl. ¶ 5, p. 4).

40. Dr. Robinson did not define the terms C_{max} and AUC, and their significance was not discussed.

41. Because Table 3, which reports "Mean C_{max}" and "Mean $AUC_{0\text{-}tlast}$" levels, is described by Dr. Robinson as showing "a summary of the systemic levels of DHEA and DHEA-S, we assume these terms relate to the levels of DHEA and DHEA-S in the systemic circulation. (*See* Robinson Decl. ¶ 5, Table 3, p. 4).

42. Dr. Robinson did not indicate what levels of DHEA and DHEA-S in the systemic circulation would have been expected by those in the art.

43. Dr. Robinson stated:

> In conclusion, inhalation exposure of dogs to DHEA-S for 13 weeks, at dosages up to 3.54 mg/kg/day was well tolerated and produced no treatment-related clinical signs or changes in electrocardiogram, ophthalmology, hemograms, serum biochemistry and urinalysis parameters. Slight decreases in body weights and food consumption were noted during the treatment period. There were no changes in organ weights, macroscopic and microscopic evaluation. Based on slight changes in body weight observed, the highest dose of 3.54 mg/kg/day, which is about 90 times more than our current highest dose administered to human lungs, was considered to be the no observed adverse effect level. Increases in hematocrit, glucose and muscle mass would be expected if a significant systemic effect was observed. Furthermore, changes in pituitary, adrenal glands and sex organs would be expected if a systemic effect was produced by aerosol administration.

(Robinson Decl. ¶ 5, p. 5).

44. Dr. Robinson did not cite to any support for these expectations.

45. Dr. Robinson discussed a second study, reported to be "a randomized repeat-dose, single-blind, placebo-controlled, dose-ascending safety, tolerability and PK study of DHEA-S (once daily) with parallel groups receiving placebo and inhaled budesonide (twice daily) for 13 days in a healthy elderly population." (Robinson Decl. ¶ 6, p. 5).

46. Dr. Robinson did not explain what budesonide is, but we assume it is a different asthma drug, used for comparison with DHEA-S.

47. Dr. Robinson discussed the dosing regime of the patients receiving DHEA-S, wherein

> [e]ach DHEA-S capsule contained 25 mg of material (DHEA-S plus lactose), which includes 6.25 mg of active DHEA-S drug substance of which ~1.7 mg is in the respirable range. So, 10 capsules would deliver a maximum of approximately 17 mg of active ingredient to the lung. The number of DHEA-S capsules per cohort was 1, 2, 5 and 10.

(Robinson Decl. ¶ 6, p. 6).

48. Table 6 of Dr. Robinson's Declaration reports "ng/mL mean (range)" levels of DHEA-S and DHEA in the groups of patients receiving placebo, 1, 2, 5, or 10 capsules, as well as the normal range of DHEA-S and DHEA levels. (Robinson Decl. ¶ 6, Table 6, p. 7).

49. Dr. Robinson stated:

> TABLE 6 has the summary of circulating levels of DHEA-S exposure after 13 days of repeat dosing. One patient in the 10 capsule group had two values in a 24 hour profile that were greater than 5600 ng/mL value, however, this patient's average value was well within the normal range. All values from all other patients were in the normal range. DHEA (the first metabolite of DHEAS) levels remained constant. So, an increase in circulating levels of DHEA was not observed.

(Robinson Decl. ¶ 6, p. 7).

50. Dr. Robinson also summarized the results reported in Tables 7 and 8, by stating:

> The effect of 13 days of DHEA-S administration on cortisol responses and on sex hormone levels was also examined. DHEA-S is a C19 adrenal steroid and it can be metabolized to testosterone or estradiol. As shown in Table 7, the levels of testosterone and estradiol were unchanged, as any changes were within the normal day-to-day assay variability. For estradiol, the functional sensitivity of the estradiol assay (i.e. the lowest level at which the CV of the assay is 20%) is 15 pg/mL. Many of the subjects had estradiol levels lower than this. Therefore,

> while mean estradiol levels on day 13 in the 10CAP group might appear higher than baseline, the difference of only ~7 pg/mL is not clinically meaningful as differences of this magnitude could also be seen with repeated measures of the same sample. The data suggest that there is no dose-response relationship between the active drug and testosterone or sex hormone binding globulin (SHBG).
>
> Table 7 shows the mean 24 hour concentrations of sex hormones at baseline and at the end of dosing by group. Note only women had estradiol measured and only men had testosterone measured. Both genders had SHBG determinations. Table 8 contains the normal ranges.

(Robinson Decl. ¶ 6, p. 7).

51. Dr. Robinson discussed the results of a different study in comparison to the results of the second study reported in her declaration, by stating:

> When DHEA is administered via the systemic route, a decrease in cortisol levels is observed, see Adebowale, Ph. D., Office of Clinical Pharmacology and Biopharmaceutics, Results of adrenal function testing with Cortrosyn® (synthetic ACTH) stimulation following dosing of GL701 at a dose of 200 mg once daily for 28 days. However, following inhalation of DHEA-S, no such decrease in cortisol was observed on either baseline levels or post-ACTH stimulation levels after 13 days of dosing of DHEA-S at 1, 2, 5, or 10 capsules/day.

(Robinson Decl. ¶ 6, p. 8).

52. Dr. Robinson did not provide a report of the study by Adebowale to which she referred or any information on how "GL701 at a dose of 200 mg once daily for 28 days" compared to the doses of DHEA-S administered in her study. Nor did she provide raw data on the cortisol levels of patients in her own study.

53. Dr. Robinson concluded: "In summary, 40 normal elderly volunteers were dosed with DHEA-S, placebo, or budesonide in this safety study. Although increases in DHEAS C_{max} and AUC above baseline levels were observed, there were no adverse effects on pulmonary function, cortisol levels, sex hormones or clinical laboratory parameters of potential clinical concern." (Robinson Decl. ¶ 6, p. 8).

54. As far as we understand, no raw data of DHEAS C_{max} and AUC for the study of the 40 normal elderly volunteers was provided in Dr. Robinson's Declaration.

55. Dr. Robinson did not provide any evidence supporting whether those in the art would have expected "adverse effects on pulmonary function, cortisol levels, sex hormones or clinical laboratory parameters of potential clinical concern" given the increases in DHEAS C_{max} and AUC that were seen.

56. Dr. Robinson discussed a second study, which she stated "demonstrated the efficacy of respirable DHEA-S in the treatment of asthma with minimal systemic side effects." (Robinson Decl. ¶ 7, p. 8).

57. In this study, Dr. Robinson reported that "[p]atients were randomized to one of 2 treatment sequences (DHEA-S/placebo or placebo/DHEA-S). Each treatment period lasted for 5 days with a minimum 3 week washout between sequences. Patients received 25 mg DHEA-S or placebo once daily with the Pari® nebulizer." (Robinson Decl. ¶ 7, p. 9).

58. Dr. Robinson reported:

> Five days of daily dosing of DHEA-S was safe and well-tolerated in mild asthmatics. . . . Also, no effect on androgenic parameters was observed. 24 hour average concentration of testosterone with DHEA-S was 572 $\pm$ 191 ng/mL and with

> placebo was 593 ± 214 ng/mL. 24 hr average concentration sex hormone binding globulin (SHBG) with DHEA-S was 30.3 ± 10.7 ng/mL and with placebo was 32 ± 12 ng/mL.

(Robinson Decl. ¶ 7, p. 10).

59. Dr. Robinson did not point to any evidence supporting whether those in the art would have expected there to be an effect on adrenergic parameters under the conditions of this study.

60. Dr. Robinson concluded:

> Overall, all three studies demonstrate that inhalation of small particle size DHEA-S produces minimal systemic side effects. This is an unexpected result as it would be expected that the greater access to the systemic circulation in the lungs would cause systemic absorption and result in systemic side-effects such as modified levels of sex hormones and/or adverse effects on the sex organs. Unexpectedly, minimal systemic side effects were observed and a beneficial effect on asthma was observed.

(Robinson Decl. ¶ 8, p. 12).

III. ISSUES

The issues are:

(1) Whether Appellant has shown that the Examiner erred in rejecting claims 160-162 as being unpatentable under 35 U.S.C. § 103(a) over the combination of the teachings of Prendergast, Lieberman, and Remington.

(2) Whether Appellant has shown that the Examiner erred in rejecting claims 187-189 as being unpatentable under 35 U.S.C. § 103(a) over the combination of the teachings of Prendergast, Lieberman, Remington, and Kelly.

(3) Whether Appellant has shown that the Examiner erred in rejecting claims 160-162, 165, and 187-190 as being unpatentable under 35 U.S.C.

§ 103(a) over the combination of the teachings of Nyce, Lieberman, Remington, and Kelly.

IV. LEGAL PRINCIPLES

To determine whether subject matter would have been obvious, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. . . . Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

Under the Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), the analysis of obviousness "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 1741. Thus, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.* at 1740.

"In cases involving overlapping ranges, [the Federal Circuit and the Court of Customs and Patent Appeals] have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). *See also In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005).

A prima facie case of obviousness is not defeated merely because a claimed composition possesses a property not disclosed in the prior art. *See In re Dillon,* 919 F.2d 688, 693 (Fed. Cir. 1990). Indeed, "[p]roducts of identical chemical composition can not have mutually exclusive properties." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). Accordingly, use of a claimed composition, such as a pharmaceutical, to treat a disease different from that reported in the prior art is not necessarily nonobvious.

Appellants can argue against a prima facie case when there is a "teaching away" from a combination of references, but "[a] statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex LLC v. Apotex, Inc.* 407 F.3d 1371, 1380 (Fed. Cir. 2005).

The Applicant may rebut a prima facie case of obviousness by clear and convincing evidence of unexpected results. "When an applicant seeks to overcome a prima facie case of obviousness by showing improved performance in a range that is within or overlaps with a range disclosed in the prior art, the applicant must 'show that the [claimed] range is *critical,* generally by showing that the claimed range achieves unexpected results relative to the prior art range.' . . . Furthermore, it is well settled that unexpected results must be established by factual evidence." *In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) (quoting *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990)). In addition, "[w]hen an article is said to achieve unexpected (i.e. superior) results, those results must logically be shown as superior *compared* to the results achieved with other articles. . . . Moreover, an applicant relying on comparative tests to rebut a prima facie case of

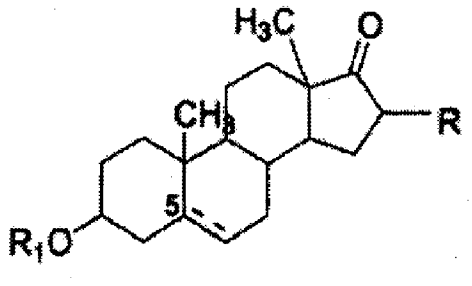
obviousness must compare his claimed invention to the closest prior art." *In re DeBlauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

V. ANALYSIS

Claims 160-162 – Prendergast, Lieberman, and Remington

Appellant's claim 160 recites:

> A pharmaceutical composition, comprising a carrier and an amount of an active agent effective for treatment of bronchoconstriction, lung inflammation, lung allergy, or asthma selected from dehydroepiandrosterone, or pharmaceutically or veterinarily acceptable salts thereof, the dehydroepiandrosterone having the chemical formula



(I);

> wherein the broken line represents a single or double bond; R is hydrogen or halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R_1 is SO_2OM, wherein M is H,
>
> wherein the pharmaceutical composition comprises particles of about 1.0 μm to about 5 μm in size.

(FF[3] 1). Prendergast teaches the same chemical structure as recited in claim 160. (FF 14). Prendergast teaches administering this compound as an inhalation (FF 16), including as a "nasal inhalation" (FF 17). Remington

[3] Finding of Fact

teaches about inhalational drugs generally. (FF 22). Remington teaches that "particle size is of major importance in the administration of this type of [inhalation] preparation. . . . It has been reported in the literature that the optimum particle size for penetration into the pulmonary cavity is of the order of ½ to 7 μm." (FF 23). Lieberman teaches that size reduction of pharmaceuticals has advantages, such as enhanced bioavailability. (FF 24).

Because Prendergast, Remington, and Lieberman all relate to pharmaceutical preparations, those of skill in the art would have had reason to use the DHEA in an inhalation formulation, as disclosed in Prendergast, at a particle size of ½ to 7 μm, as disclosed in Remington, to achieve advantages of reduced size disclosed in Lieberman.

Appellant argued against the prima facie case for obviousness by asserting "[t]here is no suggestion or motivation to combine Prendergast with Remington because Prendergast is directed mainly to systemic treatment and only mentions inhalation as part of a laundry list of treatment options." (App. Br. 5). Appellant provided Table 1, which is purported to show "a partial list of the modes of drug delivery and of pharmaceutical and medicinal agents described in Remington . . . ." (App. Br. 6). In reviewing the scope of the prior art, we do not discount a disclosure merely because it is present in a long list without particular emphasis. "To the contrary, the disclosure is prior art to the extent of its enabling disclosure." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). Prendergast teaches inhalational formulations of DHEA. (FFs 16 and 17). Thus, we see no error in combining Prendergast and Remington, where Remington teaches the particle size for such formulations (FF 23). The fact that Prendergast is said to be directed mainly to system treatment in no way

undermines the fact that it also teaches those skilled in the art alternate treatments—or as Appellant calls it "a laundry list" of alternate treatments. All treatments revealed by Prendergast, whether preferred or in "a laundry list," are in the public domain and a person skilled in the art is entitled to take advantage of each treatment option.

Appellant also argued that "Lieberman does not teach that one can routinely determine the effective particle size for a new compound by looking at the particle size of other compounds with different chemical structures." Lieberman is said to demonstrate how unpredictable and sophisticated the granulation of pharmaceuticals is. (App. Br. 7). Appellant argued further that Lieberman "teaches away from particle size below 10 μm" (*id.*), by quoting Lieberman as teaching " as 'the particle size approaches 10 μm and below, weak polarizing electrical forces called van der Waals and electrostatic forces' . . . 'inhibit powder flow through particle agglomeration.' (Lieberman, pages 32-33)" (*Id.*). Finally, Appellant cites Lieberman as teaching "'cohesive forces are strong in powders composed of particles 10 μm or less in size (Lieberman, page 35).'" (*Id.*). According to Appellant, "sections of Lieberman caution about the use of particles below 10 μm because of adverse powder properties." (*Id.*).

Lieberman does teach, though, that there are advantages to size reduction of pharmaceuticals. (FF 24). And Remington teaches that "the optimum particle size for penetration into the pulmonary cavity is of the order of ½ to 7 μm" (FF 23), while Prendergast teaches that DHEA can be used as an inhalation formulation (FFs 16 and 17). Appellant has not directed us to any portion of Lieberman that teaches that DHEA cannot be formulated to a particle size in the range taught by Remington, for the

inhalations taught by Prendergast. Nor has Appellant directed us to any other credible evidence to indicate that DHEA has a chemical structure that would not allow such a formulation. In the absence of any specific teaching relating to DHEA that would have discouraged those of skill in the art from formulating it as an inhalation comprising "particles of about 1.0 μm to about 5 μm," *see Syntex, supra.*, we see no error in the Examiner's combination of Lieberman with Prendergast and Remington.

Appellant argued that the claimed pharmaceutical composition demonstrates unexpected results, by pointing to the Robinson declaration. (App. Br. 8). Specifically, according to Appellant, the studies discussed by Dr. Robinson "unexpectedly showed the efficacy of inhaled DHEA-S in treating asthma while producing minimal adverse side effects. The unexpected results included seeing only a modest increase in circulating DHEA-S at dosages that were effective to treat asthma." (*Id.*). Appellant asserts that it is "very desirable . . . to minimize the amount of the compound that is introduced systemically due to the known undesirable side effects of the steroidal compounds." (*Id.*).

Appellant provided us with neither a copy of the Robinson Declaration in the Evidence Appendix, *see* 37 C.F.R. § 41.37(c)(1)(ix), nor any detailed explanation of, or even citation to, Dr. Robinson's declaration. In short, Appellant apparently expects us to review the declaration, and see if there is some legal or factual theory upon which we might grant relief to Appellant. We remind Appellant of the statement that "[j]udges are not like pigs, hunting for truffles buried in briefs." *See United States v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991), which was recently quoted by the Federal Circuit in *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d 1244,

1250 n.2 (Fed. Cir. 2008). Notwithstanding the shortcomings of Appellant's Brief on Appeal, we have reviewed the Robinson declaration filed during prosecution on March 14, 2005 (FF 32), and have considered it, as we understand it, looking for clear and convincing evidence of unexpected results. *See In re Heyna*, 360 F.2d 222, 228 (CCPA 1966) ("It was incumbent upon appellants to submit clear and convincing evidence to support their allegation of unexpected property."); *see also McClain v. Ortmayer*, 141 U.S. 419, 429 (1891) ("conclusive evidence" needed to establish new function); *In re Passal*, 426 F.2d 409, 412 (CCPA 1970) ("Certainly, at least, that 'clear and convincing evidence' of unexpected properties required by this court in *In re Lohr* … is lacking."); *In re Lohr*, 317 F.2d 388, 392 (CCPA 1963) ("When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed.").

Dr. Robinson presented the results of three studies of the effects of DHEA-S administered as particles sized 1-5 μm. (FF 34). In the first study, Dr. Robinson reported that dogs were administered 0, 0.25, 1.00. or 4.00 mg/kg/day DHEA-S (FF 38) by inhalation for 13 consecutive weeks (FF 37). Dr. Robinson reported various results of the "C_{max}" and "AUC" values of DHEA-S (FF 39), but did not define these terms (FF 40). We assume that they relate to levels of DHEA and DHEA-S in the systemic circulation (FF 41), though we are uncertain of the significance of these values because Dr. Robinson did not compare them to the levels of DHEA and DHEA-S in the systemic circulation that would have been expected by those in the art.

(FF 42). She only concluded: "Increases in hematocrit, glucose and muscle mass would be expected if a significant systemic effect was observed. Furthermore, changes in pituitary, adrenal glands and sex organs would be expected if a systemic effect was produced by aerosol administration." (FF 43). Dr. Robinson did not cite to any support for these expectations. (FF 44).

In the second study, healthy human volunteers inhaled DHEA-S for 13 days. (FF 45). The DHEA-S was prepared in capsules which delivered 17 mg per 10 capsules, and the patients received 1, 2, 5, or 10 capsules each. (FF 47). Levels of DHEA-S and DHEA, as well as normal levels, were provided in the declaration. (FF 48). Dr. Robinson reported: "All values from all other patients[4] were in the normal range. DHEA (the first metabolite of DHEAS) levels remained constant. So, an increase in circulating levels of DHEA was not observed." (FF 49). Dr. Robinson also concluded, from data she reported had been derived from this study, that "there is no dose-response relationship between the active drug and testosterone or sex hormone binding globin (SHBG)." (FF 50).

Dr. Robinson noted that in a study by Adebowale "a decrease in cortisol levels is observed" (FF 51), but that no similar decrease was seen in the study she was reporting (*id.*). The study by Adebowale reportedly administered "GL701 at a dose of 200 mg once daily for 28 days" (*id.*), but Dr. Robinson provided no information on how this dose compared to the doses in her study. (FF 52). Nor did she provide a copy of the actual results

[4] Dr. Robinson noted that one patient had a value of 5600 ng/mL, which she reported was "well within the normal range."

reported by Adebowale or the raw data on the cortisol levels of the patients in her own study. (*Id.*).

Finally, Dr. Robinson concluded from this second study that "[a]lthough increases in DHEAS C_{max} and AUC above baseline levels were observed, there were no adverse effects on pulmonary function, cortisol levels, sex hormones or clinical laboratory parameters of potential clinical concern." (FF 53). As far as we understand, Dr. Robinson provided no data regarding DHEAS C_{max} and AUC from this study in her declaration. (FF 54). Dr. Robinson also did not provide any evidence to support whether those in the art would have expected "adverse effects on pulmonary function, cortisol levels, sex hormones or clinical laboratory parameters of potential clinical concern" given the increases in DHEAS C_{max} and AUC that were seen. (FF 55).

In a third study, Dr. Robinson reported that "[p]atients were randomized to one of 2 treatment sequences (DHEA-S/placebo or placebo/DHEA-S). Each treatment period lasted for 5 days with a minimum 3 week washout between sequences. Patients received 25 mg DHEA-S or placebo once daily with the Pari® nebulizer." (FF 57). Dr. Robinson noted that "no effect on androgenic parameters was observed . . . ." (FF 58). Again, Dr. Robinson did not point to any evidence of whether those in the art would have expected there to be an effect on adrenergic parameters under the conditions of this study. (FF 59).

From these three studies, Dr. Robinson concluded:

> Overall, all three studies demonstrate that inhalation of small particle size DHEA-S produces minimal systemic side effects. This is an unexpected result as it would be expected that the greater access to the systemic circulation in the lungs would

> cause systemic absorption and result in systemic side-effects such as modified levels of sex hormones and/or adverse effects on the sex organs. Unexpectedly, minimal systemic side effects were observed and a beneficial effect on asthma was observed.

(FF 60).

"The Board has broad discretion as to the weight to give to declarations offered in the course of prosecution." *In re American Acad. of Science Tech Center*, 367 F.3d 1359, 1368 (Fed. Cir. 2004). In light of the content of Dr. Robinson's declaration and lack of side effects reported by others, including those with no apparent interests in this case,[5] we do not do not find the Robinson Declaration to be either clear or convincing.

First, it is not altogether clear *on this record* that the compound tested by Dr. Robinson falls within the scope of claim 160. Dr. Robinson reported using "dehydroepiandrosterone-sulfate (DHEA-S)." (FF 34). Dr. Robinson did not define the structure of "DHEA-S." Appellant's specification defines "dehydroepiandrosterone sulphate"[6] as including a sulphatide group, depicted as

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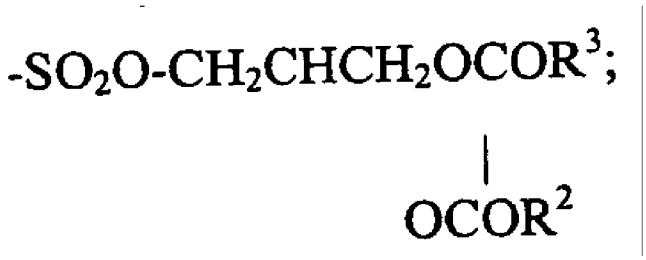
[5] Appellant reported the real party-in-interest in this case to be East Carolina University, but Epigenesis Pharmaceuticals, Inc. is listed on the cover page of the application. (FF 13). Dr. Robinson reported that she is the Vice President of Clinical Development at Epigenesis Pharmaceuticals, L.L.C. (FF 33). It is unclear if Dr. Robinson has an interest in the current application. *See Ferring B.V. v. Barr Laboratories, Inc.*, 437 F.3d 1181, 1187 (Fed. Cir. 2006) ("A witness's interest is always pertinent to his credibility and to the weight to be given to his testimony, and relevant interests are not limited to direct financial interests.").

[6] Appellant's specification does not define "dehydroepiandrosterone sulfate" and we assume it is the same as "dehydroepiandrosterone sulphate."



(FFs 7 and 8). Claim 160 does not include a compound with a sulphatide group because R_1 in claim 160 defined as SO_2OM where M is H (hydrogen) and cannot be the group depicted above. (FF 1). We do not know whether Dr. Robinson uses "sulfate" with a hydrogen as M or whether she, like the specification, is referring to a compound where M is the structure depicted above. Thus, because the compound used by Dr. Robinson is not necessarily a compound within the scope of claim 160, we cannot find clear and convinced evidence of unexpected results.

We are also not convinced that these results would have been unexpected when the claimed compound, formulated as 1-5 μm particles, was administered because Dr. Robinson did not provide any studies that compared this particle size to any other. Thus, we are not convinced that it is the particle size that produced the reportedly unexpected results and that the claimed range is critical. *See Geisler, supra.* Furthermore, tests presented to rebut a prima facie case of obviousness "must compare [the] claimed invention to the closest prior art," *DeBlauwe*, 736 F.2d at 705. but Dr. Robinson provided no comparison at all.

Dr. Robinson based her conclusions of the "minimal adverse effects" on the "modest increase in circulating DHEA-S" observed (FF 36), but she did not report what level of increase in circulating DHEA-S would have been expected by those in the art. Nor did she provide any support, such as citation to references, for her observation that those in the art would have

expected there to have been greater adverse effects from inhalation of the claimed compounds.

In fact, Prendergast reports a lack of adverse side effects when compounds that are related to the claimed compounds are administered to patients. In Example 9 of Prendergast dehydroepiandrosterone, or "DHEA," was administered orally to patients for up to six months at 100-600 mg per day. (FF 19 and 20). Though DHEA differs from the DHEA-S used by Dr. Robinson (*see* FF 15), and is also not claimed, we have no reason to believe it is less relevant to the claimed compounds than DHEA-S is. Prendergast reported that "[d]ehydroepiandrosterone . . . demonstrated a complete lack of adverse physical, biochemical or hematological effects in twelve subjects who received daily doses of up to 600 mg for up to six months." (FF 21). Considering this result, we are less inclined to be convinced by Dr. Robinson's conclusion that the absence of adverse effects upon inhalation of DHEA-S is unexpected. Stated in other terms, we credit the pre-filing date observation of Prendergast over the post-filing date observations of Dr. Robinson.

Even Appellant's own specification seems to contradict Dr. Robinson's conclusions. In the "Description of the Background," Appellant lists the "[m]ild androgenic effects, hirsutism, and increased libido" as side effects observed with DHEA treatment (FF 9), but also provides that these can be "overcome by monitoring the dose and/or by using analogues" (*id.*). Appellant does not elaborate on the doses or analogues that would alleviate these side effects. (FF 10). Dr. Robinson did not indicate that the doses and analogues she used in the studies provided in her declaration differed from those known before Appellant's filing to alleviate these side effects. Dr.

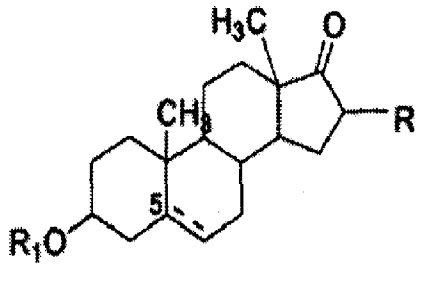
Robinson referred only to "[i]ncreases in hematocrit, glucose and muscle mass . . . changes in pituitary, adrenal glands and sex organs . . . " (FF 43), as the expected adverse effects. Given Appellant's recitation of the known adverse effects and the known ways to avoid them, we are less certain that the lack of adverse effects recited by Dr. Robinson would have been unexpected. In addition, Appellant mentioned that "long term administration of DHEA" is associated with chronic heart failure (FF 11), but, again, the length of such "long term administration" was not discussed. This effect was not mentioned by Dr. Robinson.

In light of Dr. Robinson's testimony and the evidence of Prendergast and Appellant's specification, we are not persuaded that there is clear and convincing evidence of unexpected results in the studies reported by Dr. Robinson. Thus, Appellant has not shown that the Examiner erred in rejecting claim 160 under 35 U.S.C. § 103(a) over Prendergast, Lieberman, and Remington.

Claims 187-189 – Prendergast, Lieberman, Remington, and Kelly

Appellant's claim 187, the representative claim for this rejection, recites:

> A pharmaceutical composition, comprising a carrier and an amount of an active agent effective for treatment of bronchoconstriction, lung inflammation, lung allergy, or asthma selected from dehydroepiandrosterone, or pharmaceutically or veterinarily acceptable salts thereof, the dehydroepiandrosterone having the chemical formula



(I);

> wherein the broken line represents a single or double bond; R is hydrogen or halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R1 is SO_2OM, wherein M is H
>
> wherein the pharmaceutical composition comprises particles about 15 μm to about 500 μm in size.

(FF 2). As discussed above, Prendergast, Remington, and Lieberman teach the claimed compound, administration as an inhalation, and particles of a particular, reduced size that are advantageous for delivery as inhalation pharmaceuticals. In addition, Kelly, which relates to aerosol delivery of drugs (FF 25), teaches that "devices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35 μm in diameter." (FF 26). This size range overlaps the claimed particle size range of "about 15 to about 500 μm." Thus, the combination of Prendergast, Remington, Lieberman, and Kelly teach the claimed pharmaceutical composition. *See Peterson, supra.*

Appellant argued that "the obviousness of compounds at particle sizes of about 1-5μm does not support the obviousness of compounds at about 15-500μm." (App. Br. 12). Appellant argued further that "[a] range of 1-5μm is distinct from the range of 15-500 μm, so the teaching of one range, if

anything, would teach away from the other." (*Id.*). The teaching of one range does not "teach away" from another "absent clear discouragement of that combination." *Syntex,* 407 F.3d at 1380. Appellant has not directed us to any specific teaching that would discourage formulating particles of 15-500 μm. Furthermore, Kelly teaches that "[d]evices for delivering therapeutic aerosols generate particles with aerodynamic diameters form 0.5 to 35 μm in diameter," (FF 26), providing an overlapping disclosure in the prior art as discussed above. Accordingly, we do not find Appellant's argument persuasive.

According to Appellant, "[o]ne aspect of the Examiner's argument appears to be that since past examples can be found of making pharmaceuticals in a wide range of particle sizes in the past then particles of any new compound with a size within these past ranges is obvious." (App. Br. 12). Appellant argued that "an argument by the Examiner that particle sizes is [sic] known for a past pharmaceuticals is not sufficient to make this particular size range for this particular set of compounds obvious." (App. Br. 12). The Supreme Court noted, though, that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 127 S.Ct. at 1740. Because Prendergast teaches that the claimed compound can be administered by inhalation, and Lieberman, Remington, and Kelly teach particle size reduction to produce pharmaceuticals, in general, and the claimed particles sizes, in specific, we see no error in the Examiner's rejection.

Finally Appellant argued that "the Examiner's argument that Kelly teaches introduction into the lungs does not provide the motivation to combine the references so as to make compounds of the present invention in the size range of about 15-500μm obvious." (App. Br. 13). We disagree. Upon learning that the claimed compound can be administered by inhalation from Prendergast, we see sufficient reason for those in the art to have looked to Kelly , which relates to "Aerosol Therapy for Asthma" (FF 25), and to Remington and Lieberman for the teachings discussed above.

Because Appellant has not provided any evidence of unexpected results or other secondary considerations regarding the subject matter claimed in claim 187, the Examiner did not err in rejecting claim 187 under 35 U.S.C. § 103(a) over Prendergast, Remington, Lieberman, and Kelly.

Claims 160-162, 165, 187-190 – Nyce, Lieberman, Remington, and Kelly

Nyce relates to the administration of ubiquinone to combat chronic heart failure in cancer patients treated with dehydroepiandrosterone. (FF 27). The dehydroepiandrosterone compounds taught in Nyce are the same as those claimed. (FF 28). Nyce teaches that the compounds can be made in formulations "suitable for . . . nasal . . . administration." (FF 30; *see also* FF 31). The teachings of Lieberman, Remington, and Kelly have been discussed above. Those of skill in the art would have reason to combine Nyce with Lieberman, Remington, and Kelly because after learning that dehydroepiandrosterone and ubiquinone could be administered as a nasal spray from Nyce, it would seem reasonable to look to Lieberman, Remington, and Kelly for teachings regarding formulation of drugs in the appropriate particle sizes.

Appellant argued that "[a]s in Prendergast, Nyce gives a laundry list of potential modes of treatment with DHEA, this list of methods does not provide a teaching with respect to any particular particle size range." (App. Br. 13-14). As we noted above, we do not discount a specific teaching of Nyce merely because it includes other teachings. *See Perricone, supra.* One skilled in the art is entitled to use all teachings. Nyce teaches administration as a nasal spray and so was appropriately included in the Examiner's rejection.

As Appellant also argued that "Lieberman makes it clear that the selection of a specific particle size of a pharmaceutical formulation is not routine, and depends on many factors including the chemical composition of the pharmaceutical itself. Therefore it would not be obvious to formulate the compounds of the present invention in the claimed size ranges." (App. Br. 14). As explained above, Appellant has not directed us to any specific teaching in Lieberman that the claimed compounds cannot be formulated in the claimed particle sizes and so has not persuaded us the combination of references does not render the claimed compositions obvious.

Finally, in regard to claims 165 and 190, Appellant argued that "Nyce does not address adenosine depletion, and adenosine depletion is not described in Lieberman, Remington, and Kelly. Therefore the use of ubiquinone in amounts effective to reduce adenosine depletion is not obvious in view of the cited references." (App. Br. 15). Appellants do not provide any evidence, though, that the "amount of ubiquinone . . . effective to reduce adenosine depletion," as claimed, differs from the amount of ubiquinone taught in Nyce. In fact, Appellant's specification teaches administering ubiquinone in amounts up to "about 1200 mg/kg body weight

per day" (FF 6), while Nyce also teaches that "[t]he ubiquinone is preferably administered in a total amount per day of about 1 to 1200 mg/kb/body weight . . . . (FF 29). In the absence of evidence that the amount claimed by Appellant differs from that taught by Nyce, we are not persuaded that the claimed pharmaceutical composition is not obvious.

Appellant has not demonstrated that the Examiner erred in rejecting claims 165 or claim 190 under 35 U.S.C. § 103(a) over the combination of Nyce, Lieberman, Remington, and Kelly.

VI. ORDER

Upon consideration of the record, and for the reasons given,

the Examiner's rejection of claims 160-162 under 35 U.S.C. § 103(a) over Prendergast, Lieberman, and Remington is AFFIRMED;

the Examiner's rejection of claims 187-189 under 35 U.S.C. § 103(a) over Prendergast, Lieberman, Remington, and Kelly is AFFIRMED; and

the Examiner's rejection of claims 160-162 and 187-188 under 35 U.S.C. § 103(a) over Nyce, Lieberman, and Kelly is AFFIRMED.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

qsg

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